Lilly Announces Updates to the Zyprexa and Symbyax U.S. Labels

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INDIANAPOLIS, Oct 05, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- Eli Lilly and Company announced today that as a part of on-going discussions with the U.S. Food and Drug Administration (FDA), the company has updated the Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl) U.S. product labels. This new labeling information is available at www.Zyprexa.com and www.Symbyax.com.

The updates reflect recently completed pooled analyses of Lilly's clinical trial data in adults and adolescents(1), information from two large non-Lilly studies of atypical antipsychotics (CATIE and CAFE) and discussions with the FDA. Specifically, the changes include new warnings for weight gain and hyperlipidemia (elevation of triglycerides and cholesterol) and updated information in the warning for hyperglycemia (elevated blood sugar), including additional language on a greater association of increases in glucose levels with olanzapine than with some other atypical antipsychotics. Lilly continues to work with the FDA and will provide additional data and analyses as they become available.

"Today's communication is part of Lilly's historical and ongoing commitment to inform doctors and patients about updated prescribing information," said Sara Corya, M.D., global medical director, Lilly. "Zyprexa is an important treatment option for patients suffering from the devastating effects of schizophrenia and bipolar disorder, as is Symbyax for patients with bipolar depression. This information will continue to help healthcare professionals evaluate and make the best treatment decisions for individual patients," she added.

Information on the potential risks of weight gain and elevations in blood sugar and lipids already exists in the Zyprexa and Symbyax labels. These meta- bolic changes and weight gain have been reported as adverse events since Zyprexa's approval in the U.S. in 1996 and Symbyax's approval in 2003. The Zyprexa and Symbyax labels also have contained the FDA-mandated antipsychotic class warning, which has recommended monitoring patients for elevated blood sugar and diabetes, since 2003.

"Lilly continues to recommend that clinicians consult expert guidelines for treating people with antipsychotics, particularly the monitoring of lipids and blood glucose, regardless of the medication prescribed," Dr. Corya said. "Over the last several years, the company has been actively informing healthcare professionals about these recommendations."

Lilly is communicating the updates to U.S. physicians via a "Dear Healthcare Practitioner" letter. The company also will notify consumer advocacy and professionally focused associations about this label change so they can provide important information to patients. Further, Lilly is in the process of communicating the data supporting the U.S. labeling updates with regulatory agencies outside the United States per local regulatory requirements.

Physicians, patients and caregivers who have additional questions may call the LillyAnswers Center at 1-800-LillyRx, or find additional information about the medications at www.zyprexa.com or www.symbyax.com.

Zyprexa Background

Zyprexa is indicated in the United States for the short- and long-term treatment of schizophrenia, acute mixed and manic episodes of bipolar I disorder, and maintenance treatment of bipolar disorder. Since Zyprexa was introduced in 1996, it has been prescribed to approximately 22 million people worldwide. Zyprexa is not approved for patients under 18 years of age.

Zyprexa is not approved for the treatment of patients with dementia- related psychosis. Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with those patients taking a placebo.

In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with Zyprexa.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Zyprexa.

While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or who have borderline increased blood glucose level. Patients

taking olanzapine should be monitored regularly for worsening of glucose control. Persons with risk factors for diabetes who are starting on atypical antipsychotics should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Significant, and sometimes very high, elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with Zyprexa. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Also, as with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

The most common treatment-emergent adverse event associated with Zyprexa in placebo-controlled, short-term schizophrenia and bipolar mania trials was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, postural hypotension, dry mouth, asthenia, dyspepsia, increased appetite and tremor.

Full prescribing information, including a boxed warning, is available at www.zyprexa.com.

Symbyax Background

Symbyax is indicated in the United States for bipolar depression. Antidepressants can increase suicidal thoughts and behaviors in children, teens and young adults. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for worsening depression symptoms, unusual changes in behavior or thoughts of suicide. Patients and caregivers should be especially observant within the first few months of treatment or after a change in dose. Symbyax is not approved for patients under 18 years of age.

Symbyax is not approved for the treatment of patients with dementia- related psychosis. Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with those patients taking a placebo.

In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with olanzapine, a component of Symbyax.

Symbyax should not be used with an MAOI or within at least 14 days of discontinuing an MAOI. At least five weeks should be allowed after stopping Symbyax before starting an MAOI. Thioridazine should not be given with Symbyax or within at least five weeks after stopping Symbyax. Concomitant use of Symbyax in patients taking pimozide is contraindicated. Symbyax is contraindicated in patients with known hypersensitivity to the product or any component of the product.

Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing Symbyax to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking Symbyax should be monitored regularly for worsening of glucose control. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with Symbyax use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using Symbyax, is advised. Significant, and sometimes very high, elevations in triglyceride levels have been observed with Symbyax use. Significant increases in total cholesterol have also been seen with Symbyax use.

Potential consequences of weight gain should be considered prior to starting Symbyax. Patients receiving Symbyax should receive regular monitoring of weight.

Symbyax may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some

patients, syncope, especially during the initial dose-titration period. Particular caution should be used in patients with known cardiovascular disease, cerebrovascular diseases, or those predisposed to hypotension.

If rash or other possibly allergic phenomena appear for which an alternative etiology cannot be determined, immediate discontinuation is recommended.

As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Also, as with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

The most common treatment-emergent adverse event associated with Symbyax in placebo-controlled clinical trials was somnolence. Other common events were weight gain, increased appetite, asthenia, peripheral edema, tremor, pharyngitis, abnormal thinking, and edema.

Full prescribing information, including a boxed warning, is available at www.symbyax.com.

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

This press release contains forward-looking statements about Zyprexa® and Symbyax®. These statements reflect management's current beliefs; however, as with any commercial pharmaceutical product there are risks and uncertainties in the process of research and development and commercialization and regulatory review. In addition, there are no guarantees that the products will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

(1) Note that Zyprexa and Symbyax are not approved for adolescents or anyone under the age of 18.

Zyprexa® (olanzapine, Lilly)
Symbyax ® (olanzapine and fluoxetine HCl, Lilly)

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